REMARKS

Claims 1-11, 16, 18-21, 24, 25, 30-32 and 36-39 are pending in the instant application. Claims 3, 8, 9, 16, 18-21, 24-25, 30-32, 37 and 38 have been withdrawn from consideration by the Examiner. Claims 1, 2, 4-7, 10-11, 36 and 39 have been rejected. Claim 1 has been amended. Support for the amendment is provided throughout the specification, for example, at pages 32-33. No new matter has been added by the amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Election/Restrictions

The Examiner has withdrawn claims 3, 8-9, 16, 18-21, 24-25, 30-32 and 37-38 as being drawn to a nonelected invention/species. It is respectfully pointed out that the claims should only be restricted to the elected species if no generic claim is held allowable. See MPEP § 809.01 and 37 CF.R. § 1.146. Arguments set forth herein make clear that the generic claim is allowable over the cited art. Accordingly, searching of additional species is respectfully requested.

II. Rejection of Claims under 35 U.S.C. 102(b) and 35 U.S.C. 103(a)

The rejection of claims 1, 2, 4-7, 11, 36 and 39 under 35 U.S.C. 102(b) as being anticipated by Packard et al. (NEJM 2000 343:1148-1155) has been maintained.

The rejection of claims 1-2, 4-7, 10-11, 36 and 39 under 35 U.S.C. 103(a) as being unpatentable over Packard et al. (NEJM 2000 343:1148-1155) and further in view of Rao et al. (US 2003/0120134) has also been maintained.

The Examiner suggests that Packard teach the limitations of claim 1 including measuring levels of Lp-PLA2 and CRP (page 1149 'measurements' section 2nd paragraph), analyzing the risks (Table 5) and using the risks (page 1152 'discussion' section 1st paragraph, Table 5) thus meeting the limitations of claim of the instant invention.

Applicants respectfully disagree with the Examiner's characterization of the teachings of Packard.

Firstly, Table 5 of Packard does not teach combining individual risks of markers into one risk for the patient of developing CVD. The Examiner's quoting the title of Table 5 ignores teachings of Packard in its entirety, which make it quite clear individual markers were **not** combined to assess risk of CVD. Page 1150, 2nd column, 1st sentence of first full paragraph of Packard states "The INDEPENDENCE of these variables as predictors of coronary events was assessed, as

shown in Table 5…" The caption of Table 5 reads "Model 1 included the factors shown and tested the INDEPENDENCE of the factors to each other…".

Further, on page 10, line 7 of the Office Action, the Examiner states "…the models which report risks necessarily use both LpPLA2 and CRP". It is respectfully submitted that the Examiner's understanding of the models used by Packard is incorrect. Contrary to the Examiner's suggestion, the models used by Packard **do not** report risks of CVD, only the independence of variables within the model to individually and independently assess risk of CVD. Further, if the purpose of the models of Packard were to assess the risk of CVD in a patient using a combination of variables, each model as a whole would have a relative risk associated with it. However, no such information is provided in Table 5 or anywhere else in the Packard reference.

The Examiner further suggests on page 10, line 13-15 of the Office Action that "Packard teach that a model is used to calculate risks and the model uses variables including LpPLA2 and CRP (table 5). Thus the model uses a combination of risks." This conclusion, however, is incorrect. While Packard does use the model to calculate the individual and independent risks of LpPLA2 and CRP, the model of Packard does not use a combination of risks to assess CVD. The risks

associated with LpPLA2 and CRP are the output of the model used by Packard. The model used by Packard does not use this output of individual and independent risks for any further analyses. No assessment is made by Packard whatsoever of the combination of the individual risks associated with LpPLA2 and CRP with a patient's risk of CVD.

Applicants understand that terms in the claim such as "combine" and "assess" are to be given their broadest reasonable interpretation. Applicants disagree however, that cited art is also to be interpreted so broadly as to draw conclusions not drawn by the authors themselves. Packard states "The importance of our findings regarding LpPLA2 is threefold," 1st : LpPLA2 is clinically significant and its activity is related to atherosclerotic disease; 2nd: "LpPLA2 appears to be a novel risk factor that is statistically INDEPENDENT of markers of inflammation or classic risk factors."; 3rd: inhibition of LpPLA2 has biological effects making it a potential therapeutic target. Nowhere does Packard conclude that the individual and independent risks associated with LpPLA2 and CRP can be combined to assess a patient's risk of CVD.

Applicants also respectfully disagree with the comments regarding Dr. Wolfert's Declaration.

Firstly, MPEP 706.02(b) states that rejection based on 35 U.S.C. 102(b) can be overcome by persuasively arguing

that the claims are patentably distinguishable from the prior art. Dr. Wolfert's Declaration pertains directly to differences between Packard and the instant claimed invention and is directly supportive of attorney argument regarding these differences rendering the instant claimed invention patentably distinguishable over Packard. See specifically paragraphs 5 and 6 of Dr. Wolfert's Declaration.

Further, Applicants respectfully disagree with the Examiner's apparent dismissal of Dr. Wolfert's Declaration as opinion evidence because he is one of the inventors. The case law is clear; an affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone. *Ex parte Keyes*, 214 USPQ 579 (Bd. App. 1982); *In re McKenna*, 203 F.2d 717, 97 USPQ 348 (CCPA 1953). Clear from Dr. Wolfert's Declaration is that he is very experienced in clinical diagnostics and statistical analysis utilized in developing diagnostic methods and products. His understanding of the statistical models used by Packard to determine how each marker is individually and independently associated with the risk of a cardiovascular event and the differences of such analysis as compared to the instant invention using combined individual risks is based upon years of experience and education as

well as known facts of the differences of various statistical models. See paragraphs 1, 2 and 4 of Dr. Wolfert's Declaration. Further, unlike the Examiner's opinion of what Packard teaches, Dr. Wolfert's conclusion that Packard determined how each marker individually affects the risk of a cardiovascular event is consistent with Packard's own conclusions.

In an earnest effort to advance the prosecution of this case, however, Applicants have amended claim 1 to recite a method for assessing risk of Coronary Vascular Disease (CVD) in a patient which comprises measuring levels of both Lipoprotein Associated Phospholipase A2 (Lp-PLA2) and C-reactive protein (CRP) or Low Density Lipoprotein Cholesterol (LDL) in the patient, analyzing a risk associated with the level of CRP or LDL and a risk associated with the level of Lp-PLA2, and **combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2** to assess the risk of CVD in the patient. Support for these amendments are provided throughout the specification at, for example, pages 32-33.

Packard et al. does not teach combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2 to assess the risk of CVD in the patient.

Instead, Packard clearly teaches that Lp-PLA2 is an **independent** [emphasis added] predictor of coronary heart

disease, not part of a multivariate combined risk marker assessment on the risk of a coronary event.

Specifically, in the "Statistical Analysis" section of the Methods on page 1149, Packard states "We used multivariate conditional logistic-regression models to assess the **independent** [emphasis added] prognostic value of variables."

Further, in the "Results" section at the first full paragraph in column 2 at page 1150 Packard states: "The **independence** [emphasis added] of these variables as predictors of coronary events was assessed, as shown in Table 5 and Figure 1."

Finally in the last paragraph of the discussion Packard concludes from their study that "C-reactive protein, fibrinogen and the white cell count are interrelated markers . . ." while Lp-PLA2 is concluded to be "a potential risk factor that may have a direct role in atherogenesis."

Accordingly, Packard, when read in its entirety is quite clear; multivariate assessment of variables (Lp-PLA2, CRP, etc.) was to determine **independence** of the variables, and not as "a multivariate assessment on the risk of a coronary event" or "a combination of [CRP and Lp-PLA2] risk factors" as suggested by the Examiner. Packard in no way teaches **combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2** as claimed.

Accordingly, since Packard does not teach all elements of the instant claimed invention, this reference cannot anticipate the claimed invention. See MPEP 2131.

Teachings of the secondary reference of Rao et al. fails to remedy deficiencies in Packard et al. as this reference is silent with respect to the claimed step of **combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2** to assess the risk of CVD in the patient.

Thus, as the cited combination of references does not teach or suggest all claim limitations, the combination cannot render obvious the instant claimed invention. See MPEP 2143.

Withdrawal of these rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

/Kathleen A. Tyrrell/

Kathleen A. Tyrrell
Registration No. 38,350

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515